9 EXPOSURE TO NICOTINE-DERIVED N-NITROSO COMPOUNDS AND EVIDENCE AGAINST ENDOGENOUS FORMATION.

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The nitrosation of nicotine results in the formation of N-nitrosonornicotine (NNN) and 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), two potent organ-specific genotoxic carcinogens in experimental animals for the nasal cavity and lung, respectively. In addition to which, both 4-(N-nitrosomethylamino)-4-(3-pyridyl)butyric acid (iso-NNAC) and 4-(N-nitrosomethylamino)-4-(3-pyridyl)-1-butanol (iso-NNAL) are also formed, these two compounds appear to be noncarcinogenic. Considerable evidence is available to support the carcinogenic action of the nicotine-derived nitrosamines NNN and NNK in human carcinogenesis. As a result, reductions in the exposure to both NNN and NNK from all potential exposure sources should be made.

Exposure to these two compounds may result via two potential routes: (I) Exogenous exposure to preformed nicotine-derived nitrosamines present in tobacco products, and (II) endogenous formation of these N-nitroso compounds from their chemical precursors. The endogenous formation of N-nitroso compounds (but not those derived from nicotine) has been demonstrated to occur in the oral cavity, gastrointestinal and urinary tracts.

The presence of both NNN and NNK in over 200 samples of smokeless tobaccos will be reviewed together with an estimate of the exogenous exposure to these carcinogenic compounds.

The potential endogenous nitrosation of nicotine under conditions simulating the oral cavity and stomach using artificial saliva and gastric juice was investigated using both nicotine and extracts of oral tobaccos. No evidence was found to support the endogenous nitrosation of nicotine under ***in vivo*** conditions.

It is concluded that the exposure to the nicotine-derived carcinogenic N-nitroso compounds NNN and NNK results only from the use of tobacco products containing these preformed N-nitroso compounds (exogenous exposure) and not from the ***in vivo*** nitrosation of nicotine ***per se*** (endogenous exposure).

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